

**REMARKS**

Claims 1-3, 5, 7-9, 13-22, 24-31 and 33-38 are pending in the above-identified application. No amendments have been made to the claims. The amendment puts the case in a better condition to resolve matters for purposes of appeal, such that entry after final is warranted. Applicants respectfully request reconsideration of the present application in view of the following remarks.

## REJECTIONS

### Rejection of Claims 1, 5-13 and 14-18 under 35 U.S.C. 103(a) as being unpatentable over Levine US 5,635,362 (Levine '362) in view of Van Vlasselaer US 5,474,687 (Van Vlasselaer '687)

The Examiner has rejected claims 1, 5-13 and 14-18 stating, “[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the density beads of Levine with those density beads of Van Vlasselaer. One of ordinary skill would be motivated because both Levine and Van Vlasselaer teaches methods of providing accurate and reproducible cell separation layers.” Applicants respectfully traverse the rejection.

Levine '362 teaches a one-step method for determining the presence or absence of a target analyte in a biological sample using target analyte capture bodies that settle into predetermined locations within a transparent tube and labeling of the captured analyte (see col. 1, lines 8-17). Van Vlasselaer '687 teaches a method for high yield enrichment of progenitor cells based on density gradient centrifugation (see col. 5, lines 13-15). The references fail to teach Applicants claimed invention, which is a method for separating target components using a container that has a focusing device with a passage for receiving and elongating layers of the sample that are forced into the passage and beads having a density of 1.00 to 1.06 g/cc.

The Examiner has cited *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981) for the proposition that the “test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art.” The Examiner’s use of this reference is misplaced. Even if the references implicitly suggest or motivate combination, any combination of the cited references must teach all of the limitations of the claimed invention. To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. (See *In re Royka*, 490 F.2d 981, CCPA 1974.)

Levine '362, either alone or in combination with Van Vlasselaer '687, fails to teach or suggest all the limitations of the instant claims. As stated by the Examiner, Levine '362 fails to

teach the density, size and type of beads to be used in the separation. (Paper 15, page 4). Van Vlasselaer '687 also fails to teach the density of beads to be used in the separation. Van Vlasselaer '687 teaches methods of rapid and high yield enrichment of progenitor cells based on a specific density gradient centrifugation using a solution that has a density of 1.0605 g/mL. The beads of Van Vlasselaer '687 are greater than 1.08 g/ml, which is greater than those of the presently claimed invention. (See col. 11, lines 65 to col. 12, lines 1-3.) The Examiner has incorrectly focused on the density of the gradient solution in Van Vlasselaer '687 to read the bead density limitation into the instant claims.

Additionally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine the reference teachings. The motivation is lacking here because Van Vlasselaer '687 requires both a very specific gradient solution (one having a density adjusted to 1.0605 g/mL, an osmolality of 270-290 mOsm/kg H<sub>2</sub>O and a pH of 6.8-7.8) and a specially designed cell-trap centrifugation tube that traps the unwanted materials below the trap. (See col. 5, lines 13-19). This special feature teaches away from the claimed invention. It is improper to combine references where the reference teaches away from their combination. See *In re Grasselli*, 713 F. 2d 731 (Fed. Cir. 1983).

Finally, there must be a reasonable expectation of success from combining the references. The Examiner concludes that "[o]ne would have had reasonable expectation of success using beads of Van Vlasselaer with the method of Levine ['362] because both use the similar method to achieve cell separation." (Paper No. 15, page 5). As explained above, the density of the beads of Van Vlasselaer '687 are greater than the density of those in the presently claimed invention. Use of the beads of Van Vlasselaer '687 would result in the separated sample accumulating in the bottom of the tube, not in the passage that elongates and separates the sample.

The Examiner has failed to meet the criteria necessary to establish a case of *prima facie* obviousness. Van Vlasselaer '687, alone or in combination with Levine '362, lacks the necessary bead size. Reconsideration and withdrawal of the outstanding rejection is respectfully requested.

Rejection of claims 19-22, and 24-30 under 35 U.S.C. 103 (a) as being unpatentable over Levine US 5,393,674 (Levine '674) in view of Van Vlasselaer US 5,474,687 (Van Vlasselaer '687)

The Examiner has rejected claims 19-22 and 24-30 stating “[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc and size of about 4 to 5 microns as taught by Van Vlasselaer in the method of Levine et al. (US Patent 5,393,674). One of ordinary skill in the art would have been motivated to include a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06 g/cc and size of about 4 to 5 microns in the method of Levine et al. (US Patent 5,393,674) for the advantage of providing for a rapid and high yield procedures to enrich for cell of interest and processing a complete sample would not require no [sic] specialized instrumentation (Van Vlasselaer: col. 3, lines 22-28 and 43-45).” (Paper 15, page 9). Applicants respectfully traverse the rejection.

Levine '674 either alone or in combination with Van Vlasselaer '687 fails to teach or suggest all the limitations of the present claims. As stated by the Examiner, Levine '674 “does not expressly disclose that the method includes having a particular carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc and size of about 4 to 5 microns.” (Paper 15, page 8). As discussed above, Van Vlasselaer '674 teaches a specific gradient solution in combination with a specially designed tube and use of beads greater than 1.08 g/mL (See col. 11, lines 65 to col. 12, lines 1-3; claim 7). The beads of Van Vlasselaer '687 are greater than 1.08 g/mL so that unwanted materials can sink below the constriction member and allow the wanted materials to be easily decanted. (See col. 11, lines 33 – 41 and col. 11, line 65 to col. 12, line 3.) Van Vlasselaer '687 fails to teach the bead size of the present invention.

Further, the combination of Levine '674 and Van Vlasselaer '687 would render the combination of references inoperable for the intended purpose of harvesting the sample from the axial through passage because the beads of Van Vlasselaer '687 would remain below the float and prevent harvesting. The Examiner's proposal for modifying the references in an effort to

attain the claimed invention causes the references to become inoperable or destroys its intended function; therefore, the requisite motivation to make the modification does not exist. *See In re Fritch*, 972 F.2d at 1265 n.12, 23 U.S.P.Q.2d at 1783 n.12 (Fed. Cir. 1992) ("A proposed modification [is] inappropriate for an obviousness inquiry when the modification render[s] the prior art reference inoperable for its intended purpose."); *In re Ratti*, 270 F.2d 810, 813, 123 U.S.P.O. 349, 352 (C.C.P.A.1959) (holding the suggested combination of references improper under § 103 because it "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate"). Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of claims 31, and 33-36 under 35 U.S.C. 103(a) as being unpatentable over Levine US 5,393,674 (Levine '674) in view of Van Vlasselaer US 5,474,687 (Van Vlasselaer '687)

The Examiner has rejected claims 31, and 33-36 stating: "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc as taught by Van Vlasselaer in the method of Levine et al., (US Patent 5,393,674). One of ordinary skill in the art would have been motivated to include a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc in the method of Levine et al., (US Patent 5,393,674) for the advantage of providing for a [sic] rapid and high yield procedures to enrich for cell of interest and processing a complete sample would not requires no [sic] specialized instrumentation (Van Vlasselaer: col. 3, lines 22-28 and 43-45)." (Paper 15, page 12). Applicants respectfully traverse the rejection.

Levine '674 either alone or in combination with Van Vlasselaer '687 fails to teach or suggest all the limitations of the claimed invention. Applicants teach first carrier beads of the density 1.0 to about 1.06 g/cc in combination with second carrier beads. As stated by the Examiner, Levine '674 does not expressly disclose that the method includes having particulate

carrier that contains antibody with a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc. (Paper 15, page 11). As stated above, Van Vlasselaer '687 teaches a method for high yield enrichment of progenitor cells based on density gradient centrifugation (see col. 5, lines 13-15) with beads of density greater than 1.08 g/mL. The references either alone or in combination fail to teach the bead density of the claimed invention. To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. (See *In re Royka*, 490 F.2d 981, CCPA 1974.)

Further, the Examiner's reliance on *In re Keller*, 642 F.2d 413, 208, USPQ 871, (CCPA 1981) is misplaced. The combination of Levine '674 and Van Vlasselaer '687 would suggest to one skilled in the art that the beads remain *below* the float, which would render the combination of references inoperable for the claimed invention's intended purpose of harvesting sample from the float's through passage. When modifying the prior art in an effort to attain the claimed invention causes the art to become inoperable or destroys its intended function the requisite motivation to make the modification does not exist. See *In re Fritch*, 972 F.2d at 1265 n.12, 23 U.S.P.Q.2d at 1783 n.12 (Fed. Cir. 1992); *In re Ratti*, 270 F.2d 810, 813, 123 U.S. P.Q. 349, 352 (C.C.P.A.1959).

The Examiner fails to show that there is a reasonable expectation of success in the combination of Levine '674 and Van Vlasselaer '687. The Examiner states: "one of ordinary skill in the art would have expectation for success to combine Levine et al. (US Patent 5,393,674) and Van Vlasselaer (US Patent 5,474,687) because both Levine et al. (US Patent 5,393,674) and Van Vlasselaer (US Patent 5474687) disclose the method of density gradient centrifugation (Van Vlasselaer: col.: 10, lines 22-24; Levine: col. 1, lines 7-27; claim 1) (e.g. analogous art)." (Paper 15, page 13-14)." That the references disclose methods of density gradient centrifugation is an insufficient basis to suggest a reasonable likelihood of success in their combination. In moving from the prior art to the claimed invention, the Examiner cannot base his determination of obviousness on what the skilled person might try or find obvious *to try*. Rather, the proper test requires the Examiner to determine what the prior art would have led the skilled person *to do*. See *In re Dow Chem. Co. v. American Cyanamid Co.*, 837 F.2d at 473, 5 U.S.P.Q.2d at 1531. One skilled in the art would not have been motivated to use the beads of Van Vasselaer '687 because the beads would have been too heavy for the intended purpose.

The Examiner has failed to meet the criteria necessary to establish a case of *prima facie* obviousness, reconsideration and withdrawal of the outstanding obviousness rejection is respectfully requested.

Rejection of claims 1-18 under 35 U.S.C. 103(a) as being unpatentable over Levine US 5,393,674 (Levine '674) in view of Van Vlasselaer US 5,474,687 (Van Vlasselaer '687)]

Examiner rejects claims 1-18 stating: “[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to include a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc and size of about 4 to 5 microns as taught by Van Vlasselaer in the method of Levine et al., (US Patent 5,393,674). One of ordinary skill in the art would have been motivated to include a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc and size of about 4 to 5 microns in the method of Levine et al. (US Patent 5,393,674) for the advantage of providing for a rapid and high yield procedures to enrich for cell of interest and processing a complete sample would not require no [sic] specialized instrumentation (Van Vlasselaer: col. 3, lines 21-28 and 43-45) since both Levine et al. (US Patent 5,393,674) and Van Vlasselaer disclose the method of blood cell separation by centrifugation (Levine et al. (US Patent 5,393,674): col. 1, lines 7-14; fig. 1 and fig. 4; Van Vlasselaer: col. 2, lines 59-63).” (Paper 15, page 16). Applicants respectfully traverse the rejection.

Levine '674 in combination with Van Vlasselaer '687 fails to teach or suggest all the limitations of the currently pending claims. As stated by Examiner, “[t]he method of Levine '674 does not expressly disclose that the method includes having a particulate carrier that contains antibody having a binding affinity for a specific sample constituent and having a density of about 1.0 to 1.06g/cc and size of about 4 to 5 microns.” (Paper 15, page 15) Van Vlasselaer '674 teaches beads greater than 1.08 g/mL (col. 11, lines 65 to col. 12, lines 1-3; claim 7). Use of the beads of Van Vlasselaer '687, which are greater than 1.08 g/mL, would suggest to one skilled in the art that the beads remain *below* the float. This would allow the unwanted materials

to sink below the constriction member and allow the wanted materials to be easily decanted. (See col. 11, lines 33 – 41 and col. 11, line 65 to col. 12, line 3.) Van Vlasselaer '687 fails to teach the bead size of the present invention; and the combination of Levine '674 and Van Vlasselaer '687 would render the claimed invention inoperable for the intended purpose of collecting sample in the axial passage. Reconsideration and withdrawal of the outstanding obviousness rejection is respectfully requested.

Rejection of claims 37-38 under 35 U.S.C. 103(a) as being unpatentable over Levine US 5,635,362 (Levine '362) in view of Levine US 5,393,674 (Levine '674)

The Examiner has rejected claims 37-38 stating: “[i]t would have been obvious, to a person of ordinary skill in the art at the time the invention was made to include that the float have ribs and the passage is for receiving and elongating layers of the sample as taught by Levine #2 [Levine '674] in the method of Levine #1 [Levine '362].” As admitted by the Examiner Levine '362 fails to teach that the float contains ribs and the passage is for receiving and elongating layers of the sample. (Paper 15, page 18). Levine '674 fails to teach a float with ribs, instead, it teaches a float with an ‘annular sleeve’ with flared ends that *surrounds the core portion* (Levine '674; col. 4, lines 8-13, Figure 1). The Examiner states: “[o]ne of ordinary skill in the art would have been motivated to include that the float have ribs and the passage is for receiving and elongating layers of the sample in the method of Levine #1 for the advantage of providing a ten fold expansion of the white cell and platelet layers when performing the cell harvesting with the tube-float combination (Levine #2: col. 2, lines 50-60) since both Levine #1 and Levine #2 disclose the method of cell separation by density gradient centrifugation (Levine #1: col. 1, lines 9-18; Levine #2: col. 1, lines 7-14; fig. 1 and fig. 4).” (Paper 15, page 18). Applicants respectfully traverse the rejection.

As stated by the Court of Appeals for the Federal Circuit in the case of *In re Dembicza*k, 50 USPQ2d 1614 (1999):

A claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the

time the invention was made to a person having ordinary skill in the art." 35 U.S.C. Section 103(a) (Supp. 1998); see *Graham v. John Deere Co.*, 383 U.S. 1, 14, 148 USPQ 459, 465 (1966). The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. See *Graham*, 383 U.S. at 17-18, 148 USPQ at 467; *Miles Labs, Inc., Inc. v. Shandon Inc.*, 997 F.2d 870, 877, 27 USPQ2d 1123, 1128 (Fed. Cir. 1993). ...

Our analysis begins in the text of section 103 quoted above, with the phrase "at the time the invention was made." For it is this phrase that guards against entry into the "tempting but forbidden zone of hindsight," see *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 873, 228 USPQ 90, 98 (Fed. Cir. 1985), overruled on other grounds by *Nobelpharma AB v. Implant Innovations, Inc.*, 141 F.3d 1059, 46 USPQ2d 1097 (Fed. Cir. 1998), when analyzing the patentability of claims pursuant to that section. Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. See, e.g., *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 UPSQ 303, 313 (Fed. Cir. 1983). Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." Id.

Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. See, e.g., *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); *In re Rouffet*, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). See also *Graham*

, 383 U.S. at 18, 148 USPQ at 467 ("strict observance" of factual predicates to obviousness conclusion required). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability -- the essence of hindsight. See, e.g., *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). In this case, the Board fell into the hindsight trap.

We have noted that evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved, see *Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1630 (Fed. Cir. 1996), *Para-Ordinance Mfg. v. SGS Imports Intern., Inc.*, 73 F.3d 1085, 1088, 37 USPQ2d 1237, 1240 (Fed. Cir. 1995), although "the suggestion more often comes from the teachings of the pertinent references," *Rouffet*, 149 F.3d at 1355, 47 USPQ2d at 1456. The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. See, e.g., *C.R. Bard*, 157 F.3d at 1352, 48 USPQ2d at 1232. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence." E.g., *McElmurry v. Arkansas Power & Light Co.*, 995 F.2d 1576, 1578, 27 USPQ2d 1129, 1131 (Fed. Cir. 1993) ("Mere denials and conclusory statements, however, are not sufficient to establish a genuine issue of material fact."); *In re Sichert*, 566 F.2d 1154, 1164, 196 USPQ 209, 217 (CCPA 1977).

The Examiner has failed to demonstrate that there is any suggestion or motivation in the combination of Levine '362 and Levine '674 or within the knowledge of one of ordinary skill to modify or alter the references to arrive at the present claims. That the references both involve separation by centrifugation is insufficient to provide the prerequisite motivation to arrive at a ribbed float for receiving and elongating as instantly claimed. The art must still suggest the desirability of the modification.

Additionally, the Examiner fails to recite any reasonable expectation of success in combination of Levine '362 and Levine '674. Levine '362 teaches a float with cylindrical 'bands' (Levine '362; col. 7, lines 38-40; Figure 4) horizontal to the container's longitudinal axis. Levine '674 teaches a float with an 'annular sleeve' with flared ends that surrounds the core portion (Levine '674; col. 4, lines 8-13, Figure 1). Levine '674 specifically discloses the annular sleeve "will expand back outwardly into snug engagement with the tube bore" (Levine '674; col. 5, lines 3-5) after centrifugation, thus foreclosing any possibility of providing a

channel between the float and the container. The suggested combination of references are improper under § 103 because they "would require a substantial reconstruction and redesign of the elements shown in [a prior art reference] as well as a change in the basic principles under which [that reference's] construction was designed to operate". *See In re Ratti*, 270 F.2d 810, 813, 123 U.S. P.Q. 349, 352 (C.C.P.A.1959) Reconsideration and withdrawal of the outstanding obviousness rejection is respectfully requested.

### CONCLUSION

Applicants believe that the present application is now in condition to allowance. Favorable reconsideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if a telephone interview would advance the prosecution of the present application.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Jaconda Wagner (Reg. No. 42,207) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-1666 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,



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